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14. ABSTRACT

Severe bone loss commonly occurs in individuals with chronic spinal cord injury who are non-weightbearing and leads to an increased risk of lower extremity fractures. This multi-site, double-blind, randomized, placebo-controlled study evaluates the efficacy and safety of two interventions known to be anabolic to bone, parathyroid hormone and mechanical loading (provided as teriparatide and vibration) in 60 SCI individuals with low bone mass. After the first year of this project, all clinical sites have obtained regulatory approval and all preparatory work has been completed. 5 participants have been enrolled with 4 additional participants in the run-in phase of the study. No results regarding efficacy or safety of these interventions are yet available.

15. SUBJECT TERMS

Spinal cord injury, bone density, osteoporosis, teriparatide, vibration

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INTRODUCTION:

After acute spinal cord injury (SCI), individuals unable to ambulate experience rapid and profound bone loss of as much as 50% in their lower extremities over the ensuing 2-5 years. This bone loss results in their having a significantly increased risk of fracture thereafter. This study evaluates the ability of two interventions, parathyroid hormone and mechanical loading, separately and together, to increase bone mass and improve bone quality in individuals with chronic SCI and low bone mass. These interventions have previously been shown to be effective in non-disabled populations of men and post-menopausal women but not examined in individuals with SCI. In this three-arm, modified factorial design, double-blind, placebo-controlled study, 60 people with chronic SCI will receive daily teriparatide and mechanical vibration. Assessment of bone mass (by DXA scanning and quantitative computed tomography), bone quality (by finite element modeling), and bone metabolism (by serum bone markers) will be undertaken at baseline and at regular intervals during one year of treatment to permit evaluation of the efficacy of these interventions.

BODY:

Overview of Yr 1 Progress:

During the first year, it had been planned to complete all of the preparatory activities required (detailed below) at each of the three study sites prior to initiating enrollment of participants and to commence participant accrual at all sites at the overall rate of 3 participants/month. All o f the preparatory activities have been completed. However, due to a longer than anticipated regulatory review period, participant accrual has been delayed so that currently only 2 sites are currently actively involved in subject activities while the third site has just received final IRB and DOD approval and should be able to commence clinical activities immediately. Despite a delayed start, recruitment activities have been very successful. A large number of potential participants have been contacted (89) and after an initial phone screening, 22 individuals have been invited for and completed a full screening, including bone evaluation. This number of individuals screened is approximately what had been planned originally, with all clinical sites active. However, the screen failure rate in our population has been considerably higher than had been planned. Therefore, at this time, 5 participants have been randomized into the trial with 4 others in run-in. Given the initiation of our other clinical site in October and the continued success in our identifying potential participants, we anticipate being able to maintain accrual of participants to meet our original enrollment goals for years 2 and 3.

Research Accomplishments:

Initial 6 months:

The following items listed in the statement of work (SOW) for the initial 6 months of the project have all been completed:

- *Submit protocol, informed consent and other regulatory documents to the Northwestern University IRB*
- *Submit protocol, informed consent and other regulatory documents to the USAMRMC Office of Research Protections (ORP) and the Human Research Protection Office (HRPO)*
- *Contact FDA regarding need for IDE*
- *Generate source documents and templates*

- *Develop data management plan*
- *Design and test study database*
- *Develop and finalize role and responsibilities of the Medical Monitor and a monitoring plan*
- *Generate randomization sequence*
- *Obtain drug and placebo from manufacturer*
- *Develop and test vibrating platforms*
- *Develop and finalize recruitment plan*
- *Develop recruitment materials; obtain contact names from SCI registry and from practice physicians*
- *Verify operational issues related to MRI acquisition protocol at Northwestern as well as analysis protocols to be utilized by Micro MRI*

After the project had been awarded, two changes to the SOW were requested by the principal investigator and approved by DOD staff. First, Edward Hines, Jr VA Medical Center expressed strong interest in being involved in this research. As they are a designated VA center of excellence in spinal cord injury and have large patient populations in this condition, it seemed optimal to attempt to incorporate them into the project. Efforts to get regulatory approval at this site have taken considerably longer than were anticipated by the site investigator, but this has now been accomplished and study personnel hired. Secondly, the company MicroMRI, who was to analyze the bone imagine, went out of business shortly after award of this project. Consequently, this technology has been replaced by using CT imaging of bone and this change discussed and approved by DOD staff as well. Both of these changes have resulted in extensive revisions and/or additions to regulatory documents, but all is currently in place and functioning well.

Months 7-12:

For the ensuing period of participant involvement, the original SOW included the following items:

- *Identify and recruit participants: planned enrollment rate is 3 participants/month*
- *Perform all study visits, assessments and procedures as outlined in the protocol*
- *Continuous collect and monitor safety data with reporting as needed to the IRB, Medical Monitor and HRPO*
- *Collect, verify and enter all data into the database*
- *Obtain serum samples and store for batch analysis at the end of the study*
- *Collect all DXA data and enter into database*
- *Acquire all MRI data and transmit to MicroMRI for analysis (see above)*
- *Meet every 6 months with Medical Monitor to review safety reports*
- *Complete annual report to IRB and regulatory authorities*

All of the above tasks have been initiated successfully and are on-going as anticipated with the exception, as noted above, of rate of enrollment. The reduced enrollment rate has been a consequence of several factors. (1) The Edward Hines, Jr VA site did not get final regulatory approval until the end of the first year of this project; it had been expected to enroll 1-2 participants/month. (2) The Northwestern/RIC site was delayed in getting final regulatory approval and has been enrolling subjects for less than 4 months. (3) The screen failure rate has been considerably higher than anticipated (approximately 50% of prescreened subjects). Despite these issues, the Northwestern/RIC site has enrolled 5 subjects with 4 others in run-in at the end of year 1 of the project. This rate compares

favorably with the projected number of 9 participants from the clinical site over this time period. With the active involvement of the VA site during year 2 and year 3, it is anticipated that the accrual rate will increase to make up for the delayed start. Our recruitment group has been extremely successful in identifying potential participants and pre-screening them over the phone. We have identified additional rehabilitation hospitals that we have partnered with and added a recruiter to assist in these recruitment outreach efforts.

KEY RESEARCH ACCOMPLISHMENTS:

- All regulatory requirements have been met at each of the 3 sites
- All study personnel have been hired at each of the sites and is in place
- Protocol finalized at each site; randomization lists generated and all study intervention successfully labeled and prepared
- Data management plan and study database in place
- Charter for medical monitor developed and approved
- 89 potential participants contacted; 22 fully screened; 5 enrolled and 4 in run-in; 5 scheduled for screening

REPORTABLE OUTCOMES:

The project is in its earliest phases of collecting data. There are only a small number of participants that have provided baseline data; no data are available of the effects of the interventions being assessed as yet.

CONCLUSION:

This project has not progressed to the point of being able to provide any conclusions in regard to the effect of these specific interventions on bone mass or bone quality in people with spinal cord injury.

REFERENCES:

None.

APPENDICES:

None.

SUPPORTING DATA:

Baseline Data of Enrolled Participants

Demographic Data

Mean Age (yr, SD))	33.7±8.3
Sex	5M/0F
Ethnicity	4 Not Hispanic or Latino, 1 Hispanic or Latino
Race	4 Black, 1 White
BMI	24.1±2.3

Clinical Descriptors

Time post-SCI (yr, SD)	12.7±6.7
Injury Level (cervical/thoracic)	0 C/5 Th
Quadriplegic/Paraplegic	1 Quad/4 Para
Motor Complete/Incomplete	3 Complete/2 Incomplete

BMD T scores (SD)

Spine	-2.0±1.6
R Total hip	-2.7±0.8
R Femoral Neck	-2.2±1.0
L Total Hip	-3.1±0.8
L Femoral Neck	-2.5±0.8